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Original Communication

Heart, liver and spleen pathology in chronic alcohol and drug users

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Abstract

Alcohol- and drug-related deaths remain a major problem in the UK. Although the pathological findings of cardio-, hepato- and splenomegaly are frequently and empirically associated with chronic alcohol and drug use, there is limited published evidence available. This study hypothesises that organomegaly is associated with chronic substance use, and may represent a prognostic indicator. The weights of hearts, livers and spleens from 280 chronic alcoholics (CA) and 33 chronic drug users (CD) were compared to those of 291 controls. Using a forensic pathology database, CA and CD subjects were identified from 4708 autopsies (January 2003–June 2006) by identifying adult cases with no known coexistent diseases. The controls were non-substance users and previously healthy adults who died of traumatic injuries. Alcohol misuse was associated with cardiomegaly (27% vs. 19%, male CA vs. control) and hepatomegaly (38% vs. 15%). Majority of cases had only one organ affected. In CA, occurrence of hepatomegaly was associated with death at a younger age (female mean age 47 ± 9.4, $p < 0.009$, male mean age 50 ± 11.6, $p < 0.007$). This study demonstrated an association between cardiomegaly and hepatomegaly with chronic alcohol misuse and identifies the potential role of hepatomegaly as a determinant of poorer outcome in chronic alcohol misusers.

Keywords: Organ weights; Autopsy; Substance use; Organ enlargement

1. Introduction

Thirty-five percent of the Scottish population exceeds the recommended daily intake of alcohol of 4 units for men and 3 units for women.[1] In 2004, there were 2052 alcohol-related deaths in Scotland, which is an increase of 21% from the last 5 years.[2] In contrast to the problem of alcoholism, the prevalence of drug use appears to be declining in Scotland, from 55,800 in 2000 to 51,582 (about 2% of the population aged between 15 to 54 years old) in 2003.[3] Nevertheless, drug toxicity still accounted for 356 Scottish deaths in 2004.[4]

It is increasingly important to recognize the pathological findings observed in autopsy cases associated with prolonged alcohol and drugs use. The heart, liver and spleen are commonly affected organs in substance use. Chronic, excessive alcohol consumption has long been associated with cardiomyopathy, i.e. alcoholic cardiomyopathy with dilatation of the left ventricle.[5] Hepatomegaly caused by increased hepatocytes intracellular cell volume is also understood to be linked to alcohol abuse.[6] Antigenic stimulation consequent of chronic introduction of various antigens via injections has been suggested as a possible cause of splenomegaly found in some drug users.[7] Although the pathological findings of cardiomyopathy, hepatomegaly and splenomegaly are empirically and frequently linked to chronic alcohol and drug use, there is little statistical evidence of any significant relationship between substance use and heart, liver or spleen pathology.

Organ weights remain one of the fundamental benchmark used during autopsies to detect gross abnormalities. However, for findings to be reliable, reference material on which normality is defined and which is updated and relevant to the target population must be used. The

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updated tables of organ weights for the Caucasiod population, recently published by Grandmaison, Clarand and Durigon[8] is of use in this context. The released tables of normal organ weights used either body mass index (BMI) or height as a parameter of reference. The study found heart weight to be better correlated with BMI, while liver and spleen weight was better correlated with height. The present study aims to use the above stated tables of organ weight to identify and compare the association and frequency of cardiomegaly, hepatomegaly and splenomegaly between a normal population and populations of chronic alcoholics and drug users. Association of organomegaly and life-span of subjects will also be analyzed. This will allow the feasibility of using organ weights during autopsies as measurements of heart, liver and spleen pathology, as well as the effect organ pathology have on the health and life-span of chronic alcohol and drug users to be assessed.

2. Methods

The Division of Pathology (Forensic Medicine) at the University of Edinburgh coordinates the forensic medical service within the Lothian and Borders region of Scotland (estimated population, 900,000[9]). The Forensic Medicine section maintains the files of autopsy cases carried out by forensic pathologists employed by the National Health Service. For each case, information including a completed autopsy report and cause of death, as well as summaries of the patient's medical history and the circumstances of death (compiled by the Lothian and Borders Police) is retained.

Between January 2003 and June 2006, a total of 4708 autopsies were carried out on the instruction of the Procurators Fiscal in Lothian and Borders. Selection of chronic alcohol (CA) and chronic drug use (CD) cases was based on the 'certificates of the cause of death'. Those with 'chronic alcoholism', 'acute on chronic alcoholism', or 'chronic drug ab/mis/use' certified as contributing causes of death were initially included. However, cases with combined drug and alcohol use were excluded, so were those with subjects below the age of 18. All cases with cardiovascular diseases, diabetes mellitus, chronic infection, haematological disease, autoimmune disease, as well as those with any forms of malignancy were also excluded.

With regards to the non-alcoholic and non-drug user control group, selection was again based on the 'certificates of the cause of death'. All subjects selected were aged 18 or above and died of traumatic causes such as falls, road traffic collisions or suspension by ligature, with no diseases capable of causing heart, liver or spleen pathology.

Descriptive statistics were calculated for all external parameters, and the following ratios, heart weight: BMI, liver and spleen weights: height were obtained and compared between Control and CA and CD (Table 1). Abnormal organ weights in all groups were identified; reference table correlated against BMI was used to identify abnormal heart weights, while that correlated against height was used for liver and spleen weights (Table 2). The weights of the heart, liver and spleen were measured by the forensic

Table 1
Mean and standard deviation of age, height and BMI in Control, CA and CD

	Males					Females			
	Control ($n = 229$)	CA ($n = 181$)	p	CD ($n = 31$)	p	Control ($n = 62$)	CA ($n = 99$)	p	CD ($n = 2$)
Age (years)	43 ± 18	53 ± 11	0.00	31 ± 8	0.00	45 ± 19	50 ± 11	0.02	31 ± 1
Height (cm)	175 ± 7	171 ± 7	0.00	172 ± 8	(0.09)	164 ± 7	159 ± 7	0.00	163 ± 4
BMI (kg m^{-2})	25 ± 4	21 ± 4	0.00	22 ± 3	0.00	24 ± 5	23 ± 5	(0.13)	23 ± 5

p-values indicate statistical significance against Control.

Table 2
Mean and standard deviation of heart, liver and spleen weights according to height, H (cm), and BMI (kg m^{-2}) obtained from the study of Grangmaison, Clarand and Durigond[8]

	Height, H (cm)					
	Males			Females		
	$144 \leqslant H \leqslant 165$	$166 \leqslant H \leqslant 175$	$176 \leqslant H \leqslant 190$	$126 \leqslant H \leqslant 155$	$156 \leqslant H \leqslant 165$	$166 \leqslant H \leqslant 180$
Heart	344 ± 75	360 ± 75	281 ± 56	320 ± 88	308 ± 79	311 ± 67
Liver	1455 ± 370	1637 ± 369	1831 ± 384	1275 ± 321	1296 ± 331	1624 ± 380
Spleen	120 ± 51	150 ± 88	180 ± 90	122 ± 67	139 ± 79	160 ± 82
	BMI (kg m^{-2})					
	$14 \leqslant$ BMI $\leqslant 21$	$22 \leqslant$ BMI $\leqslant 24$	$25 \leqslant$ BMI $\leqslant 34$	$13 \leqslant$ BMI $\leqslant 20$	$21 \leqslant$ BMI $\leqslant 24$	$25 \leqslant$ BMI $\leqslant 40$
Heart	342 ± 58	370 ± 75	400 ± 69	287 ± 74	308 ± 68	362 ± 77
Liver	1581 ± 372	1730 ± 405	1769 ± 390	1346 ± 328	1521 ± 331	1609 ± 419
Spleen	143 ± 83	157 ± 83	175 ± 93	126 ± 70	150 ± 93	152 ± 67

pathologist responsible for the autopsy. The heart (including epicardial fat) was weighed after being dissected and washed to remove any clotted blood. The liver and spleen was weighed before any dissection was carried out. Data were analyzed using SPSS and p-values of less than 0.05 were considered statistically significant.

3. Results

CA and CD consisted of 181 male and 99 female alcoholics and 31 male and 2 female drug users, respectively. A total of 229 males and 62 female control cases were selected. Due to the small numbers of female CD subjects, statistical analysis of female CD was not done.

Fig. 1 shows the mean and standard deviation of age, height and weight of control subjects in the present study, as well that of subjects used by Grandmaison, Clarand and Durigon.[8] The mean and standard deviation of age, height, and BMI of all male and female subjects are shown in Table 1. For the male population, the mean age in CA is greater ($p < 0.001$) and that in CD is lower ($p < 0.001$) than Control. Female CA has a greater mean age compared to Control ($p < 0.018$).

3.1. Comparisons of organ weights

Descriptive statistics of heart weights to BMI ratios and liver and spleen weights to height ratios in all groups are shown in Table 3. Mean heart weight to BMI ratios, liver and spleen weights to height ratios in male Control were consistently greater than that in the female control group, all having $p < 0.001$. In CA, gender differences in organ weights were found in the heart ($p < 0.001$) and spleen ($p < 0.040$).

3.2. Frequency of cardiomegaly, hepatomegaly and splenomegaly in control, CA and CD

The number of cases of cardiomegaly, hepatomegaly and splenomegaly in Control, CA, and CD are shown in Fig. 2. No cases of organomegaly was found in female CD subjects. Whilst the majority of affected cases have

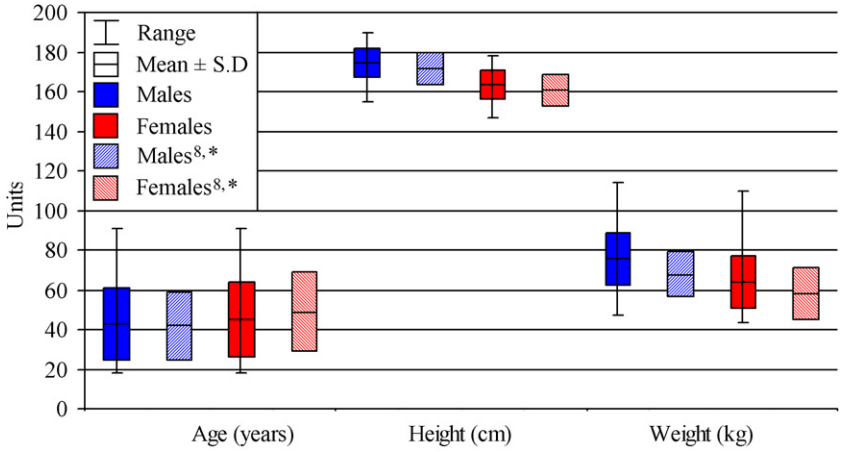

Fig. 1. Graph showing the range, mean and standard deviation of age, height and weight of male and female control subjects. Mean and standard deviation of subjects used in the study of Grangmaison, Clarand and Durigon[8] is also shown.

Table 3
Range, mean and standard deviation of heart weight to BMI ratios, and liver and spleen to height ratios in Control, CA and CD

	n	Heart weight: BMI		p	Liver weight: height		p	Spleen weight: height		p
		Range	Mean ± SD		Range	Mean ± SD		Range	Mean ± SD	
Males										
Control	229	8.3–36.2	16.1 ± 3.2	–	5.3–26.3	9.8 ± 2.4	–	0.3–3.1	1.0 ± 0.4	–
CA	181	9.4–53.5	18.5 ± 5.6	0.00	2.2–24.4	10.8 ± 3.6	0.01	0.2–8.6	1.0 ± 0.9	0.00
CD	31	13.5–25.9	17.5 ± 3.2	0.02	5.1–14.2	10.1 ± 1.8	(0.09)	0.3–1.7	1.1 ± 0.4	(0.06)
Females										
Control	62	7.5–20.9	12.7 ± 2.6	–	4.9–17.3	8.7 ± 2.1	–	0.2–1.3	0.8 ± 0.3	–
CA	99	9.2–25.0	14.9 ± 3.1	0.00	3.1–25.0	10.9 ± 3.8	0.00	0.2–7.8	0.9 ± 0.9	(0.29)
CD	2	13.1–15.1	14.1 ± 1.4	–	8.6–9.4	9.0 ± 0.5	–	0.6–0.9	0.8 ± 0.3	–

p-values indicate statistical significance against Control.

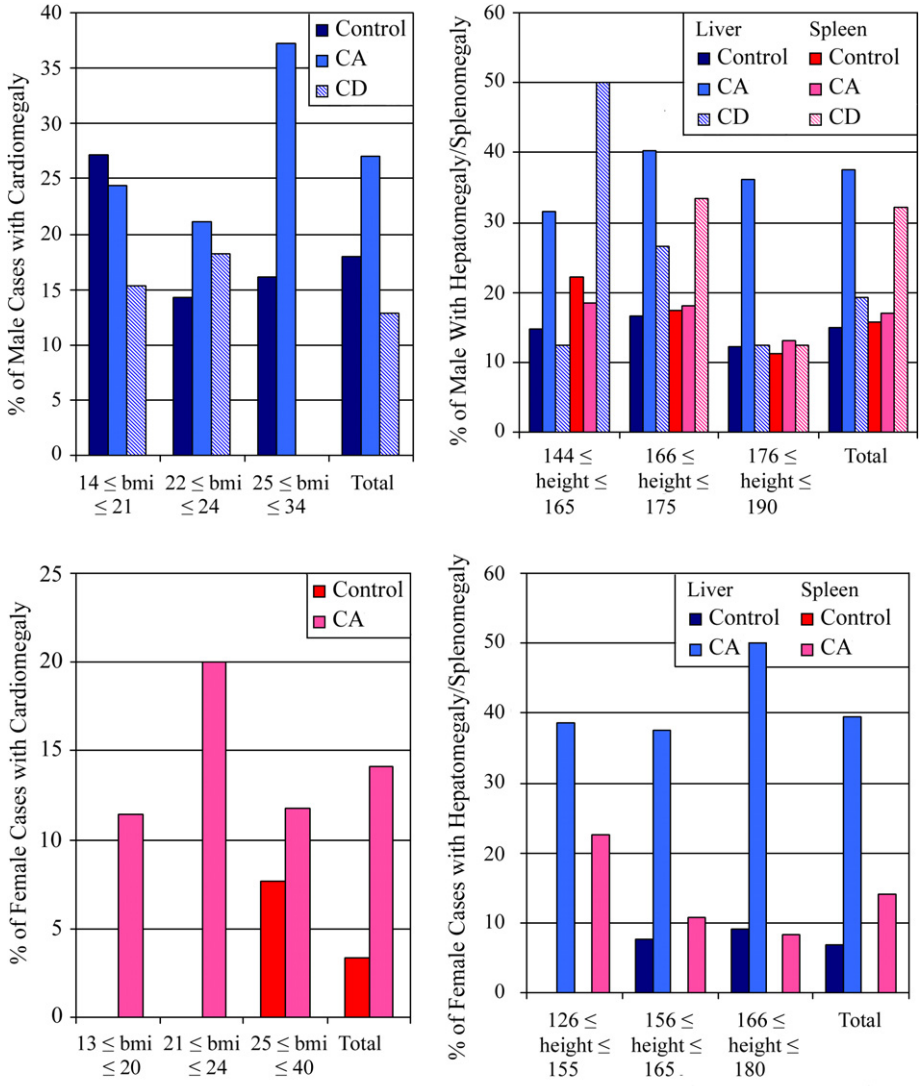

Fig. 2. Percentage frequency of cardiomyopathy in each BMI (kg m^{-2}) subgroup, and percentage frequency of hepatomegaly and splenomegaly in each height (cm) subgroup in Control, CA and CD.

enlargement of only one organ, concomitant cardiomegaly and hepatomegaly was found in 17 (9.4%) male and 6 (6.1%) female CA cases and 8 (3.5%) male Control cases. Heart and spleen enlargement was only found in male cases, with 8 (4.4%) CA and 5 (2.2%) Control cases affected. Concomitant hepatomegaly and splenomegaly is found in 8 female (8.1%) and 12 (6.6%) male CA cases, as well as 4 (12.9%) and 12 (5.2%) male CD and Control cases, respectively. Enlargement of all three organs was found in 1 (1.0%) female and 3 (1.7%) male CA cases, and 2 (0.9%) male Control cases.

The total number of cases of cardiomegaly, hepatomegaly and splenomegaly in the female CA group were significantly higher than that of the female control cases, with $p < 0.029$, $p < 0.001$ and $p < 0.001$, respectively. In the male population, cardiomegaly and hepatomegaly showed statistical relevance to alcohol abuse ($p < 0.031$ and $p < 0.001$, respectively), while splenomegaly was associated with drug use ($p < 0.041$). There were no significant difference between the number of cases of hepatomegaly and splenomegaly between male and female CA subjects. However, male CA subjects had a higher frequency of cardiomegaly when compared to female CA subjects, with $p < 0.016$.

3.3. Presence of cardiomegaly, hepatomegaly and splenomegaly and age at death

Table 4 shows the mean age of death in CA subjects with cardiomegaly, hepatomegaly and splenomegaly. There is an association between hepatomegaly and a younger age at death in males and females CA subjects, with $p < 0.007$ and $p < 0.009$, respectively (see Fig. 3). The opposite was observed in female CA subjects with cardiomegaly, and heart enlargement was associated with an increased age at death ($p < 0.029$). No association was found when analyzing cases with splenomegaly and male cases with cardiomegaly.

Table 4
Mean and standard deviation of age of CA subjects with and without heart, liver and spleen enlargement

	Heart			Liver			Spleen		
	n	Mean ± SD	*p*	*n*	Mean ± SD	*p*	*n*	Mean ± SD	*p*
Males									
Enlarged	49	54.3 ± 11.5	(0.62)	68	50.0 ± 11.6	0.01	31	51.9 ± 11.3	(0.50)
Normal	132	53.1 ± 11.2		113	55.5 ± 10.5		130	53.8 ± 11.3	
Females									
Enlarged	14	56.7 ± 10.3	0.03	39	47.4 ± 9.4	0.01	14	53.5 ± 8.6	(0.56)
Normal	85	49.2 ± 10.6		60	52.1 ± 11.4		85	49.7 ± 11.1	

p-values indicate statistical significance between cases with enlarged heart, liver or spleen against those with no evidence of organ enlargement.

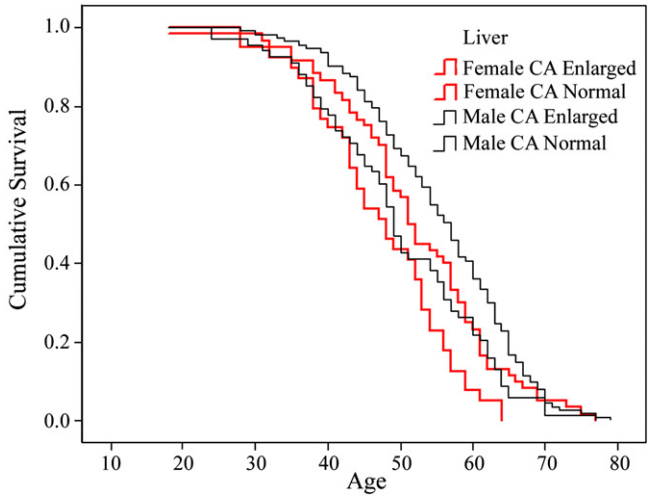

Fig. 3. Kaplan–Meier survival curve of male and female CA subjects with or without hepatomegaly.

4. Discussion

4.1. Organ weights as measure of alcohol or drug-induced pathology

The use of weight and circumstances of death as benchmarks to indicate the presence of alcohol or drug-induced cardiomyopathy, hepatomegaly and splenomegaly is valid, provided that other likely causes of heart, liver or spleen pathology are excluded. However, it is important to note that undiagnosed conditions, such as systemic hypertension, may still be present in the study population. Other important factors such as the level of physical activity of individual subjects were unknown at the time of study, and so the significance of exercise-induced hypertrophic cardiomyopathy could not be taken into account.[10] Similarly, undiagnosed or unreported cases of chronic alcoholism or chronic drug use may be present in the control group, which may be the explanation for the large range of organ weights, especially liver, in the male control group.

The reference tables of normal organ weights were obtained by analyzing a French Caucasoid population.[8] Though not identical to the present control population, the mean age and other external parameters of the reference population were likely to be sufficiently similar to the control population to warrant its use for the fair identification of organ enlargement in this study. The same study found that heart weight was more strongly correlated with BMI, while liver and spleen weights were better correlated with height, such that the respective tables of normal weights were used. Although efforts were in place to ensure organs were weighed as carefully as possible in the current study, accuracy was still a problem. Individual variation and bias when reading the dial scale can affect the weights obtained and recorded. Studies have found that heart weight increases, while liver decreases with age.[8,11,12] Conflicting results were observed for the relationship between spleen and age.[8,13] To account for this difference in mean age, comparisons of organ weights to BMI or height ratios were used instead of simply using the mean organ weights. Comparison of the number of cases of organ enlargement could be carried out fairly, irrespective of the differing mean age, with respect to the way the tables of normal organ weights were constructed.

4.2. Chronic alcoholism

Chronic alcoholism can cause morphologic alterations in virtually all organs and tissues in the body. Alcohol-induced tissue damage is said to result from the combination of associated nutritional deficiency and the direct toxic effect of ethanol metabolism.[14] The production of acetaldehyde and the microsomal ethanol oxidizing system both contribute to the oxidative stress central to the widespread tissue and organ damage, including myocyte toxicity and fatty change of the liver.[15] Organ susceptibility to alcohol toxicity varies, and this was demonstrated by a study which found that alcoholic cardiomyopathy and alcoholic hepatitis or cirrhosis were mutually exclusive.[16] The mechanism responsible remains unknown, but would explain the large proportion of subjects with enlargement of only one organ.

Alcoholic cardiomyopathy (ACM) is an acquired heart muscle disorder characterized by dilatation of the left ventricle and progressive impairment of left ventricular function in individuals with chronic, excessive alcohol consumption.[17] Increased mean heart weight to BMI ratio in CA compared to Control is similar to that found by Steinberg and Hayden,[18] who found alcoholism linked to

an increased heart weight to body weight ratio. The greater number of cases of cardiomegaly in CA compared to the control population, together with the greater mean heart weight to BMI ratio in the former, reflected the presence and frequency of ACM in the group. A higher number of cases of cardiomegaly was found in male than female CA, which differs from that found by Fernandez-Sola and Nicolas-Arfelis.[19] In their study, incidence of ACM in women and men were similar, although the former consumed far less alcohol, suggesting a greater female propensity to alcohol-induced cardiac damage. Levels of alcohol consumption by subjects in CA were not available for comparative study.

Hepatomegaly in chronic alcoholism occurs as a result of increased hepatocyte cell volume, largely resultant of increased intracellular water content, rather than increased cell number.[20] It is associated and not infrequently present with fatty change of the liver, alcoholic hepatitis and alcoholic cirrhosis. The increased number of enlarged liver in CA compared to Control, and the significantly greater mean value of liver weight to height ratios in the CA, demonstrated the association between hepatomegaly and alcohol abuse. Although liver weights to height ratios were significantly greater in male Control than in female Control, no difference in weights were found in the CA group. This might be attributed to gender differences in metabolism and susceptibility to alcohol.[21]

Portal hypertension consequent of liver disease such as cirrhosis or less commonly, massive fatty changes, are the main causes of splenomegaly in the setting of chronic alcoholism.[22] Hepatomegaly need not be present, and only 8.1% males and 6.6% females in CA had a combination of both. No relationship was found between the frequencies of splenomegaly with alcoholism in males, but one was established in females. However, mean spleen weight to height ratio was greater in male CA compared to Control.

4.3. Chronic drug misuse

Drug misuse can be defined as the use of psychoactive or performance enhancing drug in a way that differs from generally approved medical or social practices. The most commonly reported drugs in Scotland are heroin, diazepam, dihydrocodeine, methadone and cannabis, and while statistics of cocaine use remains low, the use of cocaine continues to be on the rise, from 4% (of reported illicit drug use to the Scottish Drug Misuse Database) in 2000 to 8% in 2004.[3] A study found that adult males are twice as likely to be dependent on or misuse alcohol or drugs, and that adult males had higher rates of dependency.[23]

Chronic cocaine use has been associated with both hypertrophic and dilated cardiomyopathy.[24,25] The exact mechanism is unknown, but may be associated with direct or indirect myocyte toxicity, or to adulterants and contaminants present in the drug.[26] Steatosis, a cause of hepatomegaly, is found in up to 70% of drug misusers; fatty accumulations can be microvesicular, macrovesicular or mixed, and can be consequent of viral hepatitis infection so commonly complicating chronic drug use.[27] Enlargement and congestion of the liver can also occur in the setting of acute narcotic overdose, in conjunction with pulmonary oedema. Splenomegaly in chronic drug misuse is most likely caused by recurrent intravenous injections of drugs, contaminated with antigens such as adulterants, virus and bacteria.[7] Viral antigen was found in 16% of the drug users in one study.[28]

There is no relation between chronic drug use and the number of cases of cardiomyopathy and hepatomegaly, although the mean heart weight to BMI ratio was higher in male CD compared to Control. Drug use was associated with a greater number of cases of splenomegaly in males, but with no significant difference in mean spleen weight. The latter is in contrast to a study which found mean spleen weight in chronic users approximately twice that of the control population.[29] The small numbers of CD subjects in this study might have prevented the observation of any significant trend.

4.4. Effects of organ weights on lifespan

All CA subjects with hepatomegaly had a generally shorter lifespan than those with no liver enlargement. This can be attributed to the poor prognosis of liver disease, especially cirrhosis. Five-year survival rate of severe alcoholic liver disease is 30–60%, in contrast to the 86% found in a study on ACM.[30,31] An association was found between cardiomegaly and a longer lifespan in females. However, the small number of cases of cardiomegaly in females has to be taken into account when considering this association. With respect to the results of male CA group, which involved analyzing a greater number of affected subjects, it is more likely that cardiomegaly and splenomegaly do not affect lifespan of chronic alcoholics.

5. Conclusion

There was a positive relationship between alcohol abuse and frequency of heart and liver enlargement, the latter having an effect on the lifespan of chronic alcoholics. Positive association between splenomegaly and chronic alcohol consumption was only found in the females. Chronic drug use was associated with splenomegaly in the male population, although the small numbers of chronic drug users recruited would have prevented the identification of any possible trends. This study identifies the possible role of hepatomegaly as a determinant of poorer outcome in chronic alcohol abusers. It has also demonstrated the feasibility of using organ weights to aid the identification of pathological changes and emphasized their role in providing clues when identifying chronic substance users and in establishing the cause of death during autopsies. This stresses the need for accurate measurements of organ weights

during autopsies and the importance of maintaining up to date tables of normal organ weights.

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